Complete Summary

GUIDELINE TITLE

Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin.

BIBLIOGRAPHIC SOURCE(S)

Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, Boehlecke B, Chesson AL Jr, Friedman L, Maganti R, Owens J, Pancer J, Zak R, Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007 Dec 1;30(12):1705-11. [35 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline is an update of a previously issued version (Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. Sleep 1994;17[4]:348-51).

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- October 24, 2007, Provigil (modafinil): Cephalon has agreed to include additional labeling revisions to the WARNINGS, CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Hypersomnias of central origin, including:

- Narcolepsy (with or without cataplexy, due to medical condition or unspecified)
- Idiopathic hypersomnia (with or without long sleep time)
- Recurrent hypersomnia (e.g., Klein-Levin syndrome)
- Hypersomnia due to medical condition (e.g., Parkinson's disease, myotonic dystrophy, multiple sclerosis)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pediatrics
Psychiatry
Sleep Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To present recommendations on therapy of hypersomnia of central origin
- To update previous practice parameters for the therapy of narcolepsy and to serve as the first practice parameters to address treatment of other hypersomnias of central origin

TARGET POPULATION

Adults and children diagnosed with narcolepsy and other hypersomnias of central origin

Note: This guideline excludes patients for whom daytime sleepiness is the primary complaint, but the cause of this symptom is due to disturbed nocturnal sleep or misaligned circadian rhythms.

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Management

1. Evaluation of other possible contributing causes of excessive daytime sleepiness
2. Establishment of individual treatment objectives

Treatment

1. Medications:
    - Modafinil
    - Sodium oxybate
    - Amphetamine, methamphetamine, dextroamphetamine, methylphenidate
    - Selegiline
    - Ritanserin
    - Tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, fluoxetine, reboxetine
    - Methylphenidate
    - Lithium carbonate
2. Scheduled naps
3. Regular follow-up
    - Monitor response to treatment, respond to potential side effects of medications, and enhance the patient's adaptation to the disorder
    - Determine adherence, assist the patient with occupational and social problems

MAJOR OUTCOMES CONSIDERED

- Reduction in daytime sleepiness
- Quality of life
- Adverse effects of and tolerance to medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The task force developed search terms and search strategies suitable for queries of the medical literature using Medline. Explicit inclusion and exclusion criteria were established to guide selection of relevant citations. Search terms included the names of each disorder and each medication of interest. Editorials, letters to the editor, books and book chapters, abstracts from professional meetings, review articles, publications in languages other than English, and studies involving non-human subjects were excluded.

Searches involving narcolepsy and cataplexy were performed for the period from 1999 through April 26, 2006, since the search performed for the previous treatment of narcolepsy paper in 2001 included citations through 2000. Searches involving non-narcolepsy topics were performed on April 28, 2006 with no date limit, since non-narcolepsy topics were not covered in the previous papers. A second and final search using the same search strategy was performed in October, 2006 in order to identify new articles published after the initial search.

A separate search was performed to query the medical literature with regard to medication safety issues, including adverse effects, pregnancy and breast-feeding issues, and pediatric issues. This search involved a dual strategy in which the Physicians' Desk Reference was used to identify general information about the medications of interest without regard to diagnosis. Second, the task force performed a more specific Medline search to identify articles regarding individuals who received the medications of interest, and the majority of these reports involved subjects with sleep disorders. In contrast to the strategy employed for the literature search regarding treatment a less restrictive approach was utilized, allowing for review of case reports and articles with small numbers of subjects. Our review also included all treatment articles extracted above that reported adverse events. Extractions were performed on articles that were otherwise excluded from consideration for the regular review, including those that addressed hypersomnia and fatigue in the setting of psychiatric illness and other medical conditions.

The initial Medline search performed on April 26, 2006 yielded 1,073 citations. Task force members reviewed each citation by title and abstract to ascertain whether the article was relevant and whether inclusion or exclusion criteria were met. Additional articles were considered for inclusion by searching the bibliographies of previously identified articles (a process known as pearling). The task force accepted thirty-three treatment articles for review and the remainder were rejected because the article was deemed not relevant (did not address issues in the Population, Intervention, Comparison, and Outcome [PICO] tables) or because the article contained exclusionary features. The task force identified 48 articles for the Safety search; this group includes all medication-related articles from the treatment search.

NUMBER OF SOURCE DOCUMENTS

33

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of Evidence

Level I: Randomized, well-designed trials with low alpha and beta error,* or meta-analyses of randomized controlled trials with homogeneity of result

Level II: Randomized trials with high alpha and beta error, methodologic problems, or high quality cohort studies*

Level III: Nonrandomized concurrently controlled studies (case-control studies)

Level IV: Case-control or cohort studies with methodological problems, or case series

Level V: Expert opinion, or studies based on physiology or bench research

*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or P <0.05). Beta (Type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally, trials accept a beta error of 0.20). The estimation of Type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine if sample size is adequate to find a difference in means when it is present (power generally acceptable at 80%-90%).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Relevant articles that met inclusion criteria were obtained by the American Academy of Sleep Medicine (AASM) and the full length article was made available to members of the task force using a website directory. The task force developed data extraction forms customized for this project and these forms were used to record and summarize key findings from each article identified. The task force piloted the data extraction forms on a subset of articles to identify problems with the format or content of the forms, and appropriate revisions were made.

Review of the articles and completion of the data extraction forms were performed in a two step process. Primary reviewers (individuals with doctoral level education) were identified and trained by the AASM using a standardized training module regarding use of evidence-based medicine techniques for data extraction and evidence grading. Following the initial review and data extraction process, members of the task force (secondary reviewers) reviewed each citation and data extraction form, and made corrections when necessary. Discrepancies between the primary and secondary reviewers were discussed and resolved by the task force chairman. This process is identical to that used by the AASM Standards of Practice Committee and sponsored task forces for reviewing and grading medical evidence. The task force used the Oxford Centre for Evidence-based Medicine Levels of Evidence in order to grade the strength of evidence for each citation (see the "Rating Scheme for the Strength of the Evidence" field). Evidence grading was not performed for those extractions used solely for assessing adverse effects of the medications of interest.

An Evidence Table was developed to summarize key findings from each citation. Information extracted from the safety review and general safety information from

the Physicians' Desk Reference is provided in the companion document (see the "Companion Documents" field). The evidence tables and safety review extraction tables are available online at www.aasmnet.org.

The grading of evidence was performed by an American Academy of Sleep Medicine (AASM) Task Force of content experts. Three members of the Standards of Practice Committee served as liaisons to facilitate communication between the Standards of Practice Committee and the Task Force. The Standards of Practice Committee used the evidence review of the Task Force, the prior practice parameters on narcolepsy, and the reviews upon which they were informed to develop these updated practice parameters, and rated the levels (strength) of recommendations using the AASM codification.

The Standards of Practice Committee (SPC) developed a list of specific questions and issues to be addressed in the review. This resulted in creation of Population, Intervention, Comparison, and Outcome (PICO) tables, which were used to guide the task force and to focus the review process on clinically relevant issues. The PICO tables for this project are available on the American Academy of Sleep Medicine (AASM) website directory at www.aasmnet.org. The task force reviewed prior AASM publications relevant to this topic.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Standards of Practice Committee used the evidence review of the Task Force, the prior practice parameters on narcolepsy, and the reviews upon which they were informed to develop these updated practice parameters, and rated the levels (strength) of recommendations using the American Association of Sleep Medicine (AASM) codification (see the "Rating Scheme for the Strength of the Recommendations" field).

When scientific data were absent, insufficient or inconclusive, committee consensus was used to develop recommendations at an "Option" level.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Levels of Recommendation

Standard: This is a generally accepted patient-care strategy which reflects a high degree of clinical certainty. The term standard generally implies the use of Level I Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.

Guideline: This is a patient-care strategy which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level II Evidence or a consensus of Level III Evidence.

Option: This is a patient-care strategy which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Board of Directors of the American Academy of Sleep Medicine approved these recommendations.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (**I-V**) and levels of recommendation (**standard, guideline, option**) are defined at the end of the "Major Recommendations" field.

1. An accurate diagnosis of a specific hypersomnia disorder of central origin should be established. This evaluation should include a thorough evaluation of other possible contributing causes of excessive daytime sleepiness. **(Standard)**
2. Treatment objectives should include control of sleepiness and other sleep related symptoms when present. **(Standard)**
3. The following are treatment options for narcolepsy.
    a. Modafinil is effective for treatment of daytime sleepiness due to narcolepsy **(Standard)**.
    b. Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. **(Standard)** Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. **(Option)**
    c. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. **(Guideline)**
    d. Selegiline may be an effective treatment for cataplexy and daytime sleepiness. **(Option)**
    e. Ritanserin may be effective treatment of daytime sleepiness due to narcolepsy. **(Option)**
    f. Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy. **(Guideline)**
    g. Pemoline has rare but potentially lethal liver toxicity, is no longer available in the United States, and is no longer recommended for treatment of narcolepsy. **(Option)**

h. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and reboxetine may be effective treatment for cataplexy. **(Guideline)**
i. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective treatment for treatment of sleep paralysis and hypnagogic hallucinations. **(Option)**

4. Modafinil may be effective for treatment of daytime sleepiness due to idiopathic hypersomnia. **(Option)**
5. The following medications may be effective treatments for specific types of hypersomnia due to a medical condition.
    a. Modafinil may be effective for treatment of daytime sleepiness due to Parkinson's disease. **(Option)**
    b. Modafinil may be effective for treatment of daytime sleepiness due to myotonic dystrophy. **(Option)**
    c. Methylphenidate may be effective for treatment of daytime sleepiness due to myotonic dystrophy. **(Option)**
    d. Modafinil may be effective for treatment of daytime sleepiness due to multiple sclerosis. **(Guideline)**

6. Lithium carbonate may be effective for treatment of recurrent hypersomnia and behavioral symptoms due to Kleine-Levin syndrome. **(Option)**
7. The following medications may be effective for treatment of daytime sleepiness in idiopathic hypersomnia (with and without long sleep time), recurrent hypersomnia, and hypersomnia due to a medical condition: amphetamine, methamphetamine, dextroamphetamine, methylphenidate, and modafinil. **(Option)**
8. The following are treatment recommendations previously applied to narcolepsy only. Their application is now extended to the hypersomnias of central origin covered by this practice parameter paper by committee consensus.
    a. Combinations of long- and short-acting forms of stimulants may be indicated and effective for some patients. **(Option)**
    b. Treatment of hypersomnias of central origin with methylphenidate or modafinil in children between the ages of 6 and 15 appears to be relatively safe. **(Option)**
    c. Regular follow-up of patients with hypersomnia of central origin is necessary to monitor response to treatment, to respond to potential side effects of medications, and to enhance the patient's adaptation to the disorder. **(Standard)**
        i. A patient previously stabilized on stimulant medication should be seen regularly by a health care provider at least once per year, and preferably once every 6 months, to assess the development of medication side effects, including sleep disturbances, mood changes, and cardiovascular or metabolic abnormalities.
        ii. Follow-up is necessary to determine adherence and response to treatment; to monitor for the safety of medications in individual patients; and to assist the patient with occupational and social problems.
        iii. Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and

should not operate a motor vehicle until sleepiness is appropriately controlled by stimulant medications.

iv. Of the stimulants used to treat hypersomnia of central origin, amphetamines, especially at high doses, are the most likely to result in the development of tolerance.

v. Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders that may contribute to excessive sleepiness such as insufficient sleep, inadequate sleep hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder.

vi. For side effects, dosage ranges, use in pregnancy and by nursing mothers, and contraindications, see Tables 6 and 7 in the companion guideline document (see the "Companion Documents" field).

vii. Health care providers should assist the patient with occupational and social accommodation for disabilities due to hypersomnia of central origin.

viii. Polysomnographic re-evaluation of patients should be considered if symptoms of sleepiness increase significantly or if specific symptoms develop that suggest new or increased sleep abnormalities that might occur in disorders such as sleep apnea or periodic limb movement disorder.

Definitions:

Classification of Evidence

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

The appropriate treatment of patients with narcolepsy may reduce daytime sleepiness, improve daytime alertness, allow return to normal functioning, improve quality of life, and minimize adverse effects of medication.

POTENTIAL HARMS

Side effects of medications, including sleep disturbances, mood changes, cardiovascular or metabolic abnormalities, or potential for abuse

Subgroups Most Likely to Be Harmed

Information regarding the dangers to pregnant or breastfeeding women may be found in the Physicians' Desk Reference (PDR).

CONTRAINDICATIONS

CONTRAINDICATIONS

- Amphetamine (Adderall) is not recommended for children with known structural cardiac defects; contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular (CV) disease, moderate to

severe hypertension, hyperthyroidism, h/o drug abuse, during or within 14 days of administration of monoamine oxidase (MAO) inhibitors
- Methylphenidate (Ritalin)
- Venlafaxine co-administration with MAO inhibitors is contraindicated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific care must be made by health care providers in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, Boehlecke B, Chesson AL Jr, Friedman L, Maganti R, Owens J, Pancer J, Zak R, Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007 Dec 1;30(12):1705-11. [35 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1994 (revised 2007 Dec)

GUIDELINE DEVELOPER(S)

American Academy of Sleep Medicine - Professional Association

SOURCE(S) OF FUNDING

American Academy of Sleep Medicine (AASM)

GUIDELINE COMMITTEE

Standards of Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Members: Michael Littner MD; Stephen F. Johnson MD; W. Vaughn McCall MD, MS; W. McDowell Anderson MD; David Davila MD; Kristyna Hartse PhD; Clete A. Kushida MD, PhD; Merrill S. Wise MD; Max Hirshkowitz PhD; B. Tucker Woodson MD, FACS

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The authors have indicated no financial conflicts of interest.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline is an update of a previously issued version (Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. Sleep 1994;17[4]:348-51).

GUIDELINE AVAILABILITY

Electronic copies: Available (in Portable Document Format [PDF]) from the American Academy of Sleep Medicine Web site.

Print copies: Available from the Standards of Practice Committee, American Academy of Sleep Medicine, One Westbrook Corporate Center, Suite 920, Westchester, IL 60154; Web site: www.aasmnet.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Wise MS, Arand DL, Auger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30(12):1712-27.

Electronic copies: Available in Portable document Format (PDF) from the American Academy of Sleep Medicine Web site.

Print copies: Available from the Standards of Practice Committee, American Academy of Sleep Medicine, One Westbrook Corporate Center, Suite 920, Westchester, IL 60154; Web site: www.aasmnet.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on April 25, 1999. The information was verified by the guideline developer on May 24, 1999. This summary was updated by ECRI on October 22, 2001. The update information was verified by the guideline developer as of November 21, 2001. This summary was updated by ECRI on February 11, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding Adderall and related products. This summary was updated by ECRI on November 18, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding Cylert. This summary was updated by ECRI on August 28, 2006 following the updated U.S. Food and Drug Administration advisory on Adderall. This summary was updated by ECRI on September 7, 2006 following the updated U.S. Food and Drug Administration advisory on Dexedrine. This summary was updated by ECRI Institute on April 11, 2008.

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